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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,845	06/27/2001	Xavier Paliard	1681.002	3705

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,845	PALIARD, XAVIER	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-42* is/are pending in the application.

4a) Of the above claim(s) *22-40 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-21 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 11/29/02. The Paper sequence listing and CRF submitted 11/29/02 are acknowledged and have been entered. The amendment filed 7/15/02 is acknowledged and has been entered. Claims 8 and 9 have been cancelled. Claims 1-7 and 41-42 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

Claims 22-40 and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/12/02.

It is noted that claims 26-40 and 42 were previously withdrawn from consideration. However, upon further consideration, claims 16-21 have been rejoined with the elected Invention as there is no serious search burden required to examine these additional claims. Therefore, claims 1-7, 10-21 and 41 are examined herein and claims 22-40 and 42 are withdrawn from consideration. Since the new claims have not been previously rejected, this Action can not be made final.

Response to Amendments/Arguments

The Declaration under 37 CFR 1.132 filed 7/15/02 is sufficient to overcome the rejection of claims 1-15 and 41 under 35 USC 102(a) based upon Lee et al (Hepatology 2000).

Applicant's arguments, see pages 4-6 of the paper filed 7/15/02, with respect to the rejection(s)of claim(s) under 35 USC 12, 2nd paragraph and under 35 USC 102(b) have been fully considered and are persuasive, in view of the amendments to the claims. Therefore, the rejections have been withdrawn. However, upon further consideration, new ground(s) of rejection have made for the reasons indicated herein.

With respect to the rejection of claims under 35 USC 112, 2nd paragraph, it is note that page 7 of the specification discloses:

> "Sustained expression or presence of an immunogen must be long enough for the screening of agents, preferably at least about one month in duration. Most preferably, sustained expression or presence means for the life of the animal. Germline transmission of an immunogen, however, is not included."

Therefore, the phrase "sustained expression" is not indefinite, but is in fact very broad an encompasses any expression that is long enough for screening of agents, which could be any length of time, including just a few days.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, 7 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Gorzinski et al. (Cellular Immunology, 1995, cited by Applicants).

The instant claims are drawn to a method for preparing a non-human animal, the method comprising delivering an immunogen to the liver of said animal by portal vein injection of the

imunnogen wherein the delivery is not by expression of a nucleic acid present in the germline of the animal.

Gorzinski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorzinski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.). Therefore, Gorzinski teaches a method that comprises all of the claimed method steps. Since methods comprising the same steps must have the same results, absent evidence to the contrary, the method taught by Gorzinski would result in a mouse that is tolerant to the injected immunogen.

Applicant is reminded that MPEP 2112.01 teaches "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.'"

Claims 1-3, 6, 7, 12, 13 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607).

Claims 1-3, 6, 7, 12 and 13 are drawn to a method for preparing a non-human animal, the method comprising delivering a nucleic acid encoding an immunogen to the liver of said animal

by portal vein injection of the nucleic acid encoding the imunnogen (claim 1); wherein the nucleic acid is packaged in an adeno-associated viral particle (claim 2); wherein the animal is a rodent (claim 6). It is noted that claim 3 is very broad an encompasses the administration of an immunogen to the liver of the animal. It is noted that "delivering an immunogen", given the broadest reasonable interpretation, encompasses delivering a nucleic acid encoding the immunogen.

Claim 41 is drawn to a method for preparing a non-human animal comprising delivering a nucleic acid that directs expression of an immunogen in the liver of the animal with the proviso that the nucleic acid is not present in the germ line of the animal.

Nakai teaches a method of sustained expression of a human blood coagulation factor IX in the liver of a mouse using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) in the liver of the animal wherein the adeno-associated viral particle is delivered to the liver by injection of the viral particle into the portal vein of the animal (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.). Therefore, Nakai teaches a method that comprises all of the claimed method steps. Since methods comprising the same steps must have the same results, absent evidence to the contrary, the method taught by Gorzinski would result in a mouse that is tolerant to the immunogen encoded by the injected nucleic acid.

Applicant is reminded that MPEP 2112.01 teaches "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA

1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.'"

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 10, 11 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorzinski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), and further in view of Wakita et al. (JBC, 1998, cited by Applicant).

As indicated above, Gorzinski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorzinski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorzinski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998).

Furthermore, the prior art also recognizes that sustained expression of specific HCV genes in the liver of an animal can produce immunological tolerance to the HCV gene (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of an transgenic mice results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene (i.e., HCV E1 or HCV E2) can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings based on the teaching of Wakita that an animal having sustained expression of HCV E1 or HCV E2 in the liver of an animal results in an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita). Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Claims 1, 3, 10, 11, 16, 17 , 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorzinski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), further in view of Wakita et al. (JBC, 1998, cited by Applicant) and further in view WO 97/47358 (Donnelly et al.).

As indicated above, Gorzinski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorzinski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorzinski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that sustained expression of specific HCV genes in the liver of an animal can produce immunological tolerance to the HCV gene (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice), and the HCV NS5a gene was recognized in the prior art as an HCV gene which could be used to raise an immunological response to HCV in an animal (e.g., see Donnelly et al.).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of an transgenic mice results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Donnelly specifically teaches a nucleic acid encoding the HCV NS5a gene (e.g., see Figure 12) which can be used to raise an immunological response to HCV in animal (e.g., see page 1, lines 16-21; page 3, lines 17-31; page 10, line 31 through page 1 line 35; page 20, lines 14-17; claims 1, 2, 15; etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to the HCV NS5a gene can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings and make the HCV NS5a tolerant animal based on the teaching of Wakita that an animal having sustained expression of an HCV gene in the liver of an animal results in an animal that is "a power tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita), and further in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic HCV gene. Furthermore, it would have been recognized that portal

injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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